

## Clinical and Laboratory Adverse Effects Associated with Long-Term, Low-Dose Isotretinoin: Incidence and Risk Factors

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### Abstract

**Adverse effects associated with the long-term, low-dose regimens of retinoids used in cancer chemoprevention studies are not well described. In order to examine the clinical and laboratory adverse effects of 3 years of intervention with isotretinoin (10 mg/day) and to assess potential risk factors for developing these, we collected adverse effect data on patients participating in a randomized, placebo-controlled trial designed to evaluate the effectiveness of isotretinoin in preventing the subsequent occurrence of new basal cell carcinoma. Our results showed a significantly higher incidence of adverse mucocutaneous effects and serum triglyceride elevations in the isotretinoin group ( $P < 0.001$ ). Associated risk factors included male gender, very fair skin, and elevated pretreatment triglyceride levels. The toxicity observed, although less severe and less frequent, was similar to that seen with higher doses**

**and should be weighed with adverse skeletal effects when considering long-term treatment of patients with moderate cancer risk.**

### Introduction

First marketed in 1982, isotretinoin (13-*cis*-retinoic acid), one of several synthetic derivatives of vitamin A, is currently the drug of choice for the treatment of severe recalcitrant cystic acne (1). It is also effective in the treatment of other dermatological conditions including Darier's disease, lamellar ichthyosis, and pityriasis rubra pilaris (2). More recently, isotretinoin has been under investigation to assess its chemopreventive effect in both premalignant and malignant skin disorders including non-melanoma skin cancer (3) as well as second primary regional tumors in patients with previously treated squamous cell carcinoma of the head and neck (4).

While generally effective at the doses used (0.5 to 2.0 mg/kg/day), isotretinoin has also been associated with significant adverse effects, the most common of which include drying of the skin and mucous membranes, drying of the eyes and conjunctivitis, arthralgias and myalgias, elevation of lipids and liver function tests, as well as skeletal hyperostosis following long-term therapy (5-18). These effects are usually dose related and, with the exception of skeletal hyperostoses, reversible upon discontinuation of treatment.

Because isotretinoin has been most often administered at relatively high doses, and to younger patients (less than 40 years old), the effects of long-term, low-dose isotretinoin, especially in older populations, are less well known.

We recently reported the results of a multicenter clinical trial designed to evaluate the effectiveness of a low-dose regimen of isotretinoin (approximately 0.14 mg/kg/day) administered over 3 years, in preventing new BCC<sup>3</sup> in patients at high risk for developing these skin tumors (19). Following is a report on the incidence of laboratory and clinical adverse effects observed in this

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<sup>3</sup> The abbreviations used are: BCC, basal cell carcinomas; CI, confidence interval.

population and the baseline risk factors for developing these. Findings on the adverse skeletal effects seen in this population are the subject of another article (20).

## Methods

**The Clinical Trial and Study Population.** The Isotretinoin-Basal Cell Carcinoma Prevention Trial (ISO-BCC Study) was a double-blind, randomized, placebo-controlled clinical trial conducted by the Division of Cancer Prevention and Control, National Cancer Institute (21).

Between 1984 and 1987, a total of 981 white men and women, between the ages of 40 and 75 years, were recruited and enrolled at eight clinical centers in the United States. All patients were required to have had two or more biopsy-proven BCC during the 5 years prior to randomization, normal liver and renal function, normal fasting serum cholesterol and triglyceride values ( $\leq 9$  and  $\leq 2.4$  mmol/liter, respectively), to agree not to take high-dose vitamin A ( $>5000$  units/day) for the duration of the treatment phase of the trial, and to give written informed consent prior to enrollment. In addition, women were required to be incapable of childbearing.

Patients were randomly assigned to receive either 10 mg of isotretinoin (approximately 0.14 mg/kg) or a matching placebo, (both supplied by Hoffman LaRoche, Nutley, NJ) daily, for 3 years. To monitor for skin cancer and potential adverse effects, patients reported for follow-up clinic visits at 2 weeks, 3 months, 6 months, and every 6 months thereafter for the duration of the 3 years of intervention. After the intervention phase, patients continued to be followed every 6 months for up to 2 years in order to monitor for worsening or persistent adverse effects.

Results of the study showed no protective effect of isotretinoin on the occurrence of new BCC. We found no difference in the 3-year cumulative incidence of BCC nor in the annual BCC tumor rate between the isotretinoin and placebo groups (19).

**Detection, Classification, and Management of Adverse Effects.** For the purpose of this trial, an adverse event was defined as any effect, unpleasant or harmful, that a patient might experience on either a temporary or permanent basis. All potential adverse effects, whether in the isotretinoin or placebo group, were systematically elicited, classified, managed, and documented during the course of the trial using a comprehensive approach (22). Symptoms and medical conditions present within the year preceding randomization were detected at baseline through a screening process which included the administration of a standardized symptoms questionnaire (see Appendix), a physical exam, and laboratory tests including a complete blood cell count, blood chemistries (total protein, albumin, calcium, phosphorus, creatinine, BUN, SGOT, GGT, LDH, total bilirubin, alkaline phosphatase, glucose), serum lipids (total cholesterol and triglycerides), and a urinalysis. All laboratory measurements were made at each clinical center's laboratory on samples taken after a 12-h fast. The same symptoms questionnaire was administered at all subsequent scheduled visits while laboratory tests were repeated at 2 weeks, 3 months, 12 months, and yearly through the end of the intervention phase (36 months).

New, recurrent, or worsening symptoms or abnormal

laboratory values detected at follow-up visits during the 3-year treatment period were classified in terms of their severity (as mild, moderate, severe) and association to the study medication (possibly related, remotely related, or not related) according to strict criteria (22).

Clinical management guidelines were provided to modify the dose (reduction to 5 mg/day or discontinuation of the study medication) when adverse events met specific severity criteria and were classified as "possibly related" to the study medication. All adverse events, together with their clinical course from initial detection to resolution, were recorded on appropriate data collection forms.

**Data Analysis and Statistical Methods.** All adverse effects classified as "not related" or "remotely related" to the study medication were excluded from the analyses. The  $\chi^2$  statistic was used to test proportional differences by treatment group. To assess treatment group differences between mean values, the *t* test was used (23). All reported *P* values are two-sided.

Potential risk factors for developing adverse effects were simultaneously evaluated using logistic regression analysis (24). Odds ratios and accompanying 95% test-based CI were also calculated. Baseline risk factors evaluated included: treatment group, sex, age, obesity, pretreatment fasting serum triglycerides and total cholesterol, very fair skin type, and actinic skin damage. Categories within baseline age, actinic skin damage, serum triglycerides, and total serum cholesterol were defined by median splits. Obesity was defined by a body-mass index (calculated as weight/height<sup>2</sup>) corresponding to the upper 75th percentile of the distribution, or  $\geq 27.8$ . We used skin type 1 (always burns easily, never tans) to define very fair skin in this population (25).

## Results

### Baseline Characteristics

Table 1 presents the baseline characteristics of the patient population. These characteristics did not differ between treatment groups.

### Clinical Adverse Effects

Over the 3-year intervention phase, a significantly greater percentage of patients in the isotretinoin group reported adverse effects (76%, isotretinoin; 43%, placebo;  $P < 0.001$ ). In both groups, these effects were generally mild and transient. Of the 373 patients who reported adverse effects in the isotretinoin group, 42% had their dose modified at some time during the course of the 3-year intervention, and 17% had their treatment discontinued permanently due to adverse effects. Among those taking placebo, 29% of those reporting adverse reactions had their dose modified, and 11% permanently discontinued treatment, again due to putative adverse effects.

**Mucocutaneous Effects.** Mucocutaneous reactions were the most common adverse effects observed. Although their incidence was high in both groups, the proportion in the isotretinoin group was significantly greater (70% isotretinoin; 35% placebo,  $P < 0.001$ ). Moderate to severe effects occurred in 26% of the patients reporting mucocutaneous reactions in the isotretinoin group, compared to 9% in the placebo group. Among those taking isotretinoin, chapped lips or cheilitis was by far the most

**Table 1** Baseline characteristics of the patient population by treatment group

Baseline characteristics	Isotretinoin (n = 490)	Placebo (n = 491)
Sex		
Male	367 (75) <sup>a</sup>	390 (79)
Female	123 (25)	101 (21)
Age (years)		
<63	248 (51)	241 (49)
≥63	242 (49)	250 (51)
Body mass index		
<27.8	355 (73)	372 (76)
≥27.8	132 (27)	116 (24)
Serum triglycerides (mmol/liter) <sup>b</sup>		
<1.3	250 (51)	234 (48)
≥1.3	240 (49)	257 (52)
Total cholesterol (mmol/liter) <sup>c</sup>		
<5.82	241 (49)	247 (50)
≥5.82	249 (51)	243 (50)
Skin type		
Grade I	106 (22)	106 (22)
Grade II-V	380 (78)	382 (78)
Skin actinic damage		
Mild	166 (34)	150 (31)
Moderate-severe	320 (66)	338 (69)

<sup>a</sup> Numbers in parens, percentages.<sup>b</sup> To convert triglyceride values from mmol/liter to mg/dl divide by 0.01129.<sup>c</sup> To convert cholesterol values from mmol/liter to mg/dl divide by 0.02586.

common effect, with an incidence of 44%. The incidence of other mucocutaneous effects are presented in Table 2 by treatment group.

**Arthralgias and Myalgias.** At baseline, about 75% of patients in each treatment group reported having had arthralgias and/or myalgias in the year preceding randomization. During the 3-year intervention period, 57 patients (12%) taking isotretinoin and 39 (8%) taking placebo reported either pain or stiffness of the joints and/or muscles that was considered to be "possibly related" to the study medication. This difference was only of borderline significance ( $P = 0.052$ ) (Table 2).

**Other Clinical Effects.** There was no significant treatment group difference between the percentage of patients who reported other clinical symptoms such as headache, nausea, abdominal cramps, blurred or double vision, fatigue, dizziness, depression, constipation, and diarrhea. (8% isotretinoin; 6% placebo;  $P = 0.103$ ) (Table 2).

#### Laboratory Adverse Effects

**Serum Triglycerides.** During the 3-year treatment period, adverse elevations (*i.e.*, >1.5 times the baseline value and above the upper limit of normal at each clinical center) in serum triglyceride levels were observed in a significantly greater proportion of patients taking isotretinoin. The overall incidence of adverse serum triglyceride elevations, however, was low (7% isotretinoin; 2% placebo group;  $P < 0.001$ ) (Table 3). Only two patients, both in the isotretinoin group, had elevations classified as severe. As with clinical adverse effects, adverse ele-

**Table 2** Number (%) of patients with clinical adverse effects during 3-year intervention period by category and treatment group

Category	Isotretinoin (n = 490)	Placebo (n = 491)	$P^a$
Mucocutaneous effects: overall	344 (70) <sup>b</sup>	173 (35)	<0.001
Chapped lips	215 (44)	50 (10)	<0.001
Dry skin (face/body)	139 (28)	71 (14)	<0.001
Dry mucous membranes	122 (25)	52 (11)	<0.001
Dry eyes	77 (16)	39 (8)	<0.001
Skin at fingertips/nails peeling	51 (10)	19 (4)	<0.001
Nosebleeds	30 (6)	14 (3)	0.013
Mouth sores/irritation	24 (5)	11 (2)	0.025
Other <sup>c</sup>	50 (10)	33 (7)	0.050
Arthralgias/Myalgias	57 (12)	39 (8)	0.052
Other <sup>d</sup>	41 (8)	28 (6)	0.103

<sup>a</sup> From the test for the difference between two proportions ( $\chi^2$  statistic).<sup>b</sup> Numbers in parens, percentages.<sup>c</sup> Includes symptoms such as rashes, hair loss, changes in hair texture, eczema, erythema, photosensitivity, pruritus, and psoriasis.<sup>d</sup> Includes miscellaneous symptoms such as headache, nausea, abdominal cramps, blurred or double vision, fatigue, dizziness, depression, constipation, and diarrhea.

vations in serum triglycerides were transient. In the 25 isotretinoin group patients who required a permanent reduction in dose due to adverse elevations, triglyceride values returned to normal after an average of 45 days from the start of the dose modification.

When looking at the overall change in mean triglyceride values in the study population over the 36-month intervention period, we observed a significant rise in the mean (above pretreatment levels) in both the isotretinoin and placebo group (Table 4). The total relative change from baseline was, however, lower in the placebo group (8%) compared to the isotretinoin group (24%). Mean levels in the isotretinoin group remained significantly higher than in the placebo group throughout the 36 months of treatment (Table 4).

**Liver Enzymes.** Only a small percentage of patients (3% isotretinoin; 2% placebo) developed adverse elevations in their liver enzymes (Table 3). The treatment group difference was not statistically significant ( $P = 0.289$ ).

**Total Cholesterol.** No patients in either group experienced adverse elevations in total serum cholesterol (>1.5 times the baseline value and above the upper limit of normal at each clinical center).

When looking at mean total cholesterol levels, we did observe a significant treatment group difference in the mean values starting at 2 weeks through 24 months. However, these mean levels did not rise significantly

**Table 3** Number (%) of patients with laboratory adverse effects during 3-year intervention period by treatment group

Category <sup>a</sup>	Isotretinoin (n = 490)	Placebo (n = 491)	$P^b$
Elevated triglycerides	36 (7) <sup>c</sup>	8 (2)	<0.001
Elevated liver enzymes	14 (3)	9 (2)	0.289

<sup>a</sup> Serum triglycerides and SGOT/SGPT fasting levels at least 1.5 times greater than the baseline level of the patient and exceeding the upper limit of normal at the individual clinical center.<sup>b</sup> From the test for the difference between two proportions ( $\chi^2$  statistic).<sup>c</sup> Numbers in parens, percentages.

Table 4 Mean lipid values (mmol/liter) by treatment group

Time	Serum triglycerides			Total cholesterol		
	Isotretinoin (n = 490)	Placebo (n = 491)	P <sup>a</sup>	Isotretinoin (n = 490)	Placebo (n = 490)	P <sup>a</sup>
Baseline	1.33	1.34	0.646	5.89	5.86	0.648
2 weeks	1.57 <sup>b</sup>	1.36	<0.001	5.95	5.81	0.036
3 months	1.61 <sup>b</sup>	1.41 <sup>b</sup>	<0.001	6.00	5.85	0.027
12 months	1.65 <sup>b</sup>	1.41	<0.001	6.00	5.78	0.002
36 months	1.63 <sup>b</sup>	1.45 <sup>b</sup>	<0.001	5.84	5.81	0.672

<sup>a</sup> P value for treatment group differences (from t test).<sup>b</sup> P < 0.05 compared to baseline.

above pretreatment levels during the 36 months of intervention in either treatment group (Table 4; 24-month data not shown).

### Risk Factors for Adverse Effects

**Serum Triglycerides.** Treatment with isotretinoin and pretreatment fasting serum triglyceride levels greater than 1.3 mmol/liter were the only 2 factors associated with an increased risk for developing an adverse elevation in serum triglycerides (Table 5). Treatment with isotretinoin was associated with almost a 5-fold increase in risk, while having a pretreatment fasting serum triglyceride level greater than 1.3 mmol/liter increased a patient's risk over 3-fold (Table 5).

**Mucocutaneous Effects.** Male patients and those with skin type 1 (always burns easily, never tans) had a greater than 50% increased risk of developing a mucocutaneous effect, while treatment with isotretinoin increased a patient's risk by almost 5-fold (Table 5). In subset analyses, we found that males had a greater risk for developing dry skin, dry eyes and/or dry mucous membranes (odds ratio, 1.63; 95% CI, 1.14–2.32; P = 0.007), while a skin type I was found to be more predictive for the development of chapped lips (odds ratio, 1.61; 95% CI, 1.11–2.33; P = 0.012). In addition, obese patients (body mass index  $\geq 27.8$ ) were found to be at significantly lower risk for developing chapped lips (odds ratio, 0.65; 95% CI, 0.45–0.94, P = 0.023).

### Discussion

Because this was one of the first controlled trials in which older patients were treated with long-term, very low-dose isotretinoin, we felt it most important to comprehensively elicit and document all potential adverse events and not just those considered to be drug related. While our approach may have resulted in the increased reporting of symptoms, the assessment of the history of the symptoms of each patient prior to starting treatment as well as the use of a standard method to classify both severity and causality were designed to provide a better estimate of the frequencies of isotretinoin-induced adverse effects. Furthermore, the inclusion of a placebo group in this double-blind clinical trial was key in further delineating the true incidence of adverse reactions due to isotretinoin (22). Indeed, the high incidence of putative adverse effects (43%) among placebo group patients emphasizes the need for caution when examining anecdotal or isolated case report data and underlines the importance of incorporating both a control group and a

uniform system of adverse reaction detection and classification when evaluating the toxicity of a drug.

Even at this very low dose, two of the characteristic side effects observed with higher dosage regimens of isotretinoin still manifest. Although generally milder and much less frequent, the spectrum of mucocutaneous effects among patients taking isotretinoin in this population was strikingly similar to that observed among younger patients receiving short-term therapy with similar or higher doses (5, 8–12), with chapped lips still emerging as the most frequent side effect. Similarly, our findings indicate that at this dose and length of administration, serum triglyceride levels are still significantly affected, albeit less severely and less frequently than with higher doses (5, 9, 10, 15, 16). As seen with higher dosage regimens of isotretinoin, these effects remain transient and reversible upon discontinuation of treatment, even after long-term intervention.

An important finding is the very small difference between the incidence of musculoskeletal symptoms in the treatment and control groups, as well as the lack of significant changes in total cholesterol levels. Patients included in our study were significantly older than those who normally receive isotretinoin therapy. Because joint, back, and muscular aches are often part of the aging

Table 5 Risk factors for adverse effects

Covariate	Odds ratio (95% confidence interval) <sup>a</sup>	P <sup>a</sup>
Elevated triglycerides		
Isotretinoin	4.93 (2.26–10.79)	<0.001
Male	0.78 (0.39–1.58)	0.493
Age $\geq 63$ years	0.93 (0.50–1.72)	0.811
BMI <sup>b</sup> $\geq 27.8$	1.06 (0.54–2.08)	0.872
Fasting triglycerides $\geq 1.3$ mmol/liter <sup>c</sup>	3.27 (1.58–6.78)	0.001
Fasting cholesterol $\geq 5.82$ mmol/liter <sup>c</sup>	1.01 (0.54–1.92)	0.966
Mucocutaneous effects		
Isotretinoin	4.55 (3.46–5.99)	<0.001
Male	1.59 (1.12–2.25)	0.010
Age $\geq 63$ years	1.00 (0.76–1.32)	0.986
BMI $\geq 27.8$	0.75 (0.54–1.03)	0.074
Skin type grade, 1 <sup>d</sup>	1.55 (1.11–2.17)	0.011
Actinic damage, moderate to severe	0.96 (0.70–1.31)	0.788

<sup>a</sup> P value, odds ratio, and 95% confidence interval from logistic regression analysis.<sup>b</sup> BMI, body mass index.<sup>c</sup> Pretreatment values.<sup>d</sup> Always burns easily, never tans.

process, it is possible that similar effects induced by isotretinoin might have been viewed by the patient or the evaluating clinical staff as "normal," consequently lowering the incidence rates of those effects thought to be related to isotretinoin. In addition, the heightened awareness among study participants about the recent guideline changes for evaluating and modifying cholesterol levels to decrease the risk for coronary artery disease may have played a role in encouraging patients to make dietary changes. It is unclear whether the lower incidence of some side effects and the absence of others are due to these factors or to an intrinsic difference in the effect of isotretinoin in older patients. It may well be that higher doses, rather than long-term exposure, are required for the induction of these adverse effects.

Our finding that elevated pretreatment triglyceride levels increases the risk for developing elevated triglycerides is consistent with previous reports (12, 13, 15, 26) and underscores the continued importance of evaluating this risk in patients being considered for long-term treatment with isotretinoin even at very low doses. In contrast to previous findings (12, 16), obesity was not associated with an increased risk for developing elevated triglycerides.

The increased risk for developing mucocutaneous effects among men may be explained by the more frequent use of moisturizing creams and cosmetics by women. Consequently, there may be an increased need for topical emollients in the prophylaxis and therapeutic management of these effects among men in this age group and among patients of both sexes with very fair skin. The protective effect of obesity on the development of chapped lips may be dose related. Since dosage was not adjusted to weight in this trial, heavier patients re-

ceived smaller mg/kg doses of isotretinoin, possibly attenuating its ability to induce cheilitis.

While we did not directly assess quality of life factors related to adverse effects, we did solicit the general perceptions of the patients on trial participation through a self-administered questionnaire mailed at the conclusion of the 3-year intervention period (27). Although overall, 60% of the study participants reported at least one adverse reaction during this period, only 20% cited "side effects of the study medication" as the most unpleasant aspect of study participation. Furthermore, only 3% of the subjects indicated that they felt worse as a result of their taking part in the trial.

The clinical and laboratory adverse effects of long-term, very low-dose isotretinoin, although relatively benign and predictable, must be considered in conjunction with the more serious skeletal effects seen in this older population (20). Synthetic retinoids, including isotretinoin, are currently being contemplated for clinical use as possible cancer chemopreventive agents (28). Since the potential for chronic toxicity is a major factor in evaluating the risk/benefit ratio of these drugs, the complete spectrum of side effects should be weighed when considering the long-term use of retinoids in populations with low to moderate cancer risk.

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## Appendix: Symptoms Questionnaire

Ask patient: In the last year, have you experienced [symptom]? If yes, specify severity (1 = mild; 2 = moderate; 3 = severe).<sup>a</sup> Do you currently have [symptom]? If yes, specify status (1 = onset; 2 = worsening; 3 = recurrence; 4 = continuing).<sup>b</sup>

Question	Response (yes or no)	Severity or status
1. Pain or stiffness of your joints or back? If yes, specify areas of involvement.	_____	_____
2. Loss of clumps of hair at a time?	_____	_____
3. Dry or chapped lips?	_____	_____
4. Chapped face or scaling around your nose?	_____	_____
5. Dry skin on other parts of your body? If yes, specify areas	_____	_____
6. Rashes? If yes, specify location.	_____	_____
7. Peeling skin at the end of your fingernails? <sup>c</sup>	_____	_____
8. Itching burning, reddening of your eyes?	_____	_____
9. Dryness on the inside of your nose? <sup>d</sup>	_____	_____
10. Nose bleeds?	_____	_____
11. Sore tongue or mouth?	_____	_____
12. Headaches?	_____	_____
13. Double vision or blurred vision?	_____	_____
14. Nausea or upset stomach?	_____	_____
15. Pains or cramps in your stomach?	_____	_____
16. Loose stools or watery diarrhea?	_____	_____
17. Any other problems that we haven't mentioned?	_____	_____
Specify _____		

<sup>a</sup> Asked at baseline.

<sup>b</sup> Asked at all subsequent follow-up visits.

<sup>c</sup> Includes peeling nails.

<sup>d</sup> Includes oral dryness.

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